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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/085,239	02/27/2002	Simon Ward	674569-2001	1714

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EXAMINER	
ROYDS, LESLIE A	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 02/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/085,239	WARD ET AL.	
	Examiner	Art Unit	
	Leslie A. Royds	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *40-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *See Continuation Sheet*.

DETAILED ACTION

Claims 40-42 are presented for examination.

Acknowledgment is made of Applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). The present application is recognized as a continuation-in-part of PCT/GB01/03694, which claims foreign priority to Foreign Application No. 0020531.3 filed in Great Britain. Applicant's Preliminary Amendment filed February 27, 2002 has been received and entered into the application. Accordingly, the specification at pages 4-5 has been amended to reflect the proper labeling of figures 5, 6 and 11. The specification at page 27, line 19; page 30, line 15; page 31, line 10; page 32, line 22; page 33, line 5; page 34, line 7; page 80, line 10; page 83, line 19; page 91, line 1; and page 110, line 1 has also been amended. Applicant's submission of "Appendix 1" to the specification at pages 135-145 filed February 27, 2002 has also been received and entered into the application. Applicant's sequence listing filed July 10, 2002 and September 6, 2002 have been received and entered.

Applicant's "Response to Restriction and Election of Species Requirement" filed January 13, 2005 has been received and entered into the application.

Election/Restriction

In response to the restriction and election of species requirement of September 13, 2004, Applicant has cancelled claims 1-39 drawn to non-elected subject matter and has submitted new claims 40-42, of which Applicant has requested examination on the merits. The Examiner has noted that the cancellation of claims 1-39 renders the restriction requirement previously set forth

in the Office Action dated September 13, 2004 moot and the requirement is, therefore, **withdrawn**.

Applicant's election **with traverse** of claims 40-42, drawn to methods of treating hyperproliferative diseases of the skin using inhibitors of the retinoic acid biosynthetic pathway, and the species psoriasis as the hyperproliferative skin disease and carbenoxolone as the species of retinoic acid biosynthetic pathway inhibitor, in the reply filed January 13, 2005, is acknowledged by the Examiner. The traversal is on the grounds that there are sufficiently few species recited in the claims that a search and examination of all the species at one time would not impose a serious burden on the Examiner (see page 6) and that the diseases recited in the claims comprise a proper Markush group linked by the common "structural" feature of increased proliferation and decreased differentiation and the common utility of being an inhibitor of the retinoic acid biosynthetic pathway (see last paragraph, page 6).

Applicant's traverse with respect to the election of species requirement for the hyperproliferative diseases recited in the claims has been carefully considered, but is not found to be persuasive. Although Applicant has acknowledged that each of the diseases is associated with the common "structural" feature of increased proliferation and decreased cell differentiation and the common utility of inhibiting the retinoic acid biosynthetic pathway, the Examiner has noted that the art does not necessarily recognize these eight disorders recited in the claims as sharing the common structural and common utility features as described above. Psoriasis has been recognized in the art as a condition enhanced and mediated by the release of interleukin-1,

and acne has been recognized in the art as a condition arising from and worsened by bacterial infection. Similarly, actinic keratosis, solar keratosis, ichthyoses, hyperkeratosis and Darrier's disease are all diseases associated with disorders of the keratinization process. Squamous carcinoma, on the other hand, has unknown etiology and the causes of such a condition are elusive and unpredictable. For the reasons set forth above, the diseases recited in the present claims are considered to be of four independent and patentably distinct groupings: (1) psoriasis; (2) diseases associated with keratinization (such as actinic keratosis, solar keratosis, ichthyoses, hyperkeratosis and Darrier's disease); (3) acne vulgaris; and (4) squamous carcinoma *in situ*. Each group of diseases recited above is differently searched, such that a complete and comprehensive search of the prior art for any one disease group would not necessarily result in a complete search of any one of the other disease groups based on evidence of distinct and different structural and functional features as set forth above. Therefore, the diseases recited in the present claims are considered patentably distinct and/or independent, absent factual evidence to the contrary, and a search for all four disease groups recited above would constitute an undue burden on the Examiner. The election of species requirement imposed on the diseases recited in the present claims previously set forth in the Office Action dated September 13, 2004 is maintained by the Examiner.

Applicant's traverse with respect to the election of species requirement for the retinoic acid biosynthetic pathway inhibitors has been carefully considered by the Examiner, but is also not found to be persuasive because each of the compounds, carbenoxolone, phenylarsine oxide, citral, 4-methylpyrazole, disulphiram and 3-mercaptopropionic acid, recited in the present claims

are considered to be independent and patentably distinct from one another and are capable of supporting separate patents. Although Applicant has acknowledged that each of the compounds share the common utility of being an inhibitor of the retinoic acid biosynthetic pathway, the Examiner has noted that the art does not recognize these six compounds as sharing the common utility of acting as a retinoic acid inhibitor. Furthermore, the compounds are noted to be structurally distinct from each other and have acquired a separate status in the art based upon their different classification (disulphiram: class 514, subclass 476; 4-methylpyrazole: class 514, subclass 406; phenylarsine oxide: class 514, subclass 504; citral: class 514, subclass 703; and carbenoxolone: class 514, subclass 546). Each active compound recited above is differently searched and classified, such that a complete search of the prior art for any one compound would not result in a complete search of any one of the other compounds based on evidence of distinct and different structure, function and classification as set forth above. Therefore, the six compounds recited in the present claims are considered patentably distinct and/or independent compounds, absent factual evidence to the contrary, and a search for all six compounds recited above would constitute an undue burden on the Examiner. The election of species requirement imposed on the group of compounds recited in the present claims previously set forth in the Office Action dated September 13, 2004 is maintained by the Examiner.

Allowable Subject Matter

Examination of present claims 40-42 was performed herein to the extent that the elected compound reads upon carbenoxolone and the hyperproliferative diseases treated by the instant method include psoriasis, acne vulgaris, actinic keratosis, solar keratosis, squamous carcinoma *in*

situ, ichthyoses, hyperkeratosis and disorders of keratinisation, such as Darrier's disease. A search by the Examiner determined that the use of the compound carbenoxolone for any one of the hyperproliferative skin diseases recited above, such as psoriasis, acne vulgaris, actinic keratosis, solar keratosis, squamous carcinoma *in situ*, ichthyoses, hyperkeratosis and disorders of keratinisation, such as Darrier's disease, is free of the prior art and such subject matter is, therefore, considered **allowable**.

Examination of the present claims is further expanded to the extent that the elected compound reads upon disulphiram and the hyperproliferative disease treated by the instant method reads upon psoriasis.

Specification

The Examiner has noted the incorporation by reference of Great Britain Application No. 0020351.3, filed August 17, 2000, in the disclosure at page 1, lines 2-3, and United Kingdom Application No. 9905510.5 and International Patent Application No. PCT/GB00/00876 at page 49, lines 24-25. The incorporation of essential material in the specification by reference to a foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by a statement executed by the applicant, or a practitioner representing the applicant, stating that the material being inserted is the material previously incorporated by reference and that the amendment contains no new matter. See 37 C.F.R. 1.57(f).

The Examiner has noted that the present application uses the following spelling: "disulphiram". As noted in the Napoli reference (see abstract, for example), "disulfiram" is an alternative spelling. In order to appropriately facilitate the dissemination of Applicant's presently claimed subject matter, Applicant is respectfully requested to amend the present application by adding the following phrase to the first appearance of the word disulphiram in both the specification and the claims: ---(aka disulfiram)---.

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code at page 18, line 17 and page 41, line 2. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP §608.01.

The disclosure is objected to because of the following informalities:

(i) the word "disulphiram" is misspelled at page 23, line 13 of the disclosure; the word "agitation" is misspelled at page 33, line 23 of the disclosure; and the word "epidermal" is misspelled at page 73, line 23 of the disclosure;

(ii) the phrase "Thus, the methods as described here..." should be removed at page 27, line 16 of the disclosure for clarity;

(iii) the phrase "...although are exceptions" at page 29, line 6 of the disclosure should be corrected for clarity; the phrase "...by at two..." at page 29, line 9 of the disclosure should be corrected for clarity;

(iv) the reference to "Appendix A" at page 31, line 14, is in error and should be changed to "Appendix 1";

(v) a period should be added at the conclusion of the sentence at page 32, line 18 and page 33, line 23;

(vi) the words "depression" and "cold" in line 25 of page 33 of the disclosure should not be capitalized;

(vii) the word "include" at page 57, line 3 and the word "to" at page 58, line 14 of the disclosure should be removed for clarity;

(viii) the phrase "Paragraph 1", and the like, at pages 76-80 should be concluded with a period for consistency and clarity; and

(ix) the phrase "...method according to Claim 1..." at page 120, line 18, of the disclosure should be changed to "...method according to **paragraph** 1..." since this phrase is not directly referencing the claims, but rather the previously stated paragraph at page 120, line 15 of the disclosure.

Appropriate correction is required.

Scope and Content of the Instant Claims

Claims 40-42, as filed, are drawn to methods of treating hyperproliferative diseases of the skin, such as psoriasis, acne vulgaris, actinic keratosis, solar keratosis, squamous carcinoma *in situ*, ichthyoses, hyperkeratosis and disorders of keratinization, such as Darrier's disease, by inhibiting the retinoic acid biosynthetic pathway using an inhibitor selected from carbenoxolone, phenylarsine oxide, citral, 4-methylpyrazole, disulphiram, and 3-mercaptopropionic acid.

Claim 40 is representative of a method and recites the following:

"A method of treating a hyperproliferative disease of the skin subject to treatment by inhibition of the retinoic acid biosynthetic pathway, said disease selected from the group comprising: psoriasis, acne vulgaris, actinic keratosis, solar keratosis, squamous carcinoma in situ, ichthyoses, hyperkeratosis and disorders of keratinisation, such as Darrier's disease; comprising administering, to a patient in need thereof, an inhibitor of the retinoic acid biosynthetic pathway comprising a compound selected from the group comprising: carbenoxolone, phenylarsine oxides citral, 4-methylpyrazole, disulphiram and 3-mercaptopropionic acid."

Claim 41 is representative of a method and recites the following:

"A method of treating a hyperproliferative disease of the skin subject to treatment by inhibition of the retinoic acid biosynthetic pathway, said disease selected from the group comprising: psoriasis, acne vulgaris, and hyperkeratosis; comprising administering, to a patient in need thereof, an inhibitor of the retinoic acid biosynthetic pathway comprising a compound selected from the group comprising: carbenoxolone, phenylarsine oxide, citral, 4-methylpyrazole, disulphiram and 3-mercaptopropionic acid."

Claim 42 is representative of a method and recites the following:

"A method of treating psoriasis comprising administering, to a patient in need thereof, an inhibitor of the retinoic acid biosynthetic pathway comprising a compound selected from the group comprising: carbenoxolone, phenylarsine oxide, citral, 4-methylpyrazole, disulphiram and 3-mercaptopropionic acid."

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 40-42 are rejected under 35 U.S.C. 102(b) as being anticipated by Ku et al. (U.S. Patent No. 4,870,101). Ku et al. teaches the use of pharmaceutically acceptable compounds, such as disulphiram or 2,4-di-isobutyl-6-(N,N-dimethylaminomethyl)-phenol, as inhibitors of interleukin-1 useful in controlling or treating IL-1 mediated conditions (col.1, lines 61-64), such as psoriasis, inflammation, atherosclerosis and diabetes (col.2, lines 21-23; see also col.4, claims 1 and 3).

The recitation of "...a hyperproliferative disease of the skin" in present claims 40 and 41 has been noted by the Examiner but is considered to be a descriptive limitation and fails to impart any material feature to the disease of psoriasis that is not present in the teachings of the prior art.

Although Ku et al. discloses that disulphiram is capable of inhibiting the release of interleukin-1 (col.1, lines 61-64), but is silent as to the inhibitory effects of disulphiram on the retinoic acid biosynthetic pathway as recited in the present claims 40-42, it is recognized in the art that disulphiram is a potent inhibitor of retinoic acid synthesis (see abstract of Napoli, for

example, "Retinol Metabolism in LLC-PK1 Cells", *Journal of Biological Chemistry*, 1986). Such characteristic is considered to be inherent to the compound disulphiram, despite the fact that it is not expressly disclosed in the Ku et al. reference. In concurrence with MPEP §2131.01, it is proper to rely on another reference for a rejection under 35 U.S.C. 102, provided that the additional reference is relied upon in order to show that a characteristic not expressly disclosed in the reference is inherent.

Rejection of claims 40-42 under 35 U.S.C. 102(b) is, therefore, deemed proper.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Please reference U.S. Patent No. 5,438,073 for the state of the art in dermatological compositions containing retinoids used in the treatment of psoriasis, acne, actinic keratosis, and congenital keratinization disorders.

No claims of the present application are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds whose telephone number is (571)-272-6096. The examiner can normally be reached on Monday-Friday (8:30 AM-6:00 PM), alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (571)-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Leslie A. Royds
Patent Examiner
Art Unit 1614

February 4, 2005

RAYMOND HENLEY III
PRIMARY EXAMINER
AU 1614

Continuation of Attachment(s) 6). Other: Examiner Initiated Interview Summary (PTO-413B).